



Tissue-Selective Estrogen Complex and Breast

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Although estrogen-progestin therapy has traditionally been standard care for postmenopausal women with an intact uterus experiencing bothersome menopausal symptoms, concerns about side effects related to menopausal hormone therapy (MHT) have led to a dramatic decrease in MHT use over recent decades. As many MHT side effects are now believed to be associated with the progestin component of MHT, efforts have been made to develop a progestin-free alternative to conventional MHT. Recently, a tissue-selective estrogen complex (TSEC), a combination of conjugated estrogen and bazedoxifene, was developed as a progestin-free MHT and is now approved and used worldwide for the relief of vasomotor symptoms and the prevention of bone loss in postmenopausal women. Replacement of synthetic progestin with bazedoxifene could allow more favorable safety profiles, such as those for pain or tenderness, mammographic density, and cancer incidence, for the breast. This review examined the effects of the TSEC on breasts and demonstrated evidence from preclinical and clinical studies supporting TSEC use in clinical practice.

Key Words: Bazedoxifene, Breast, Conjugated estrogen, Tissue-selective estrogen complex

INTRODUCTION

For a long period, menopausal hormone therapy (MHT) has been the gold standard for relieving vasomotor symptoms in postmenopausal women [1]. Although the main component of MHT is estrogen, progestogen should be added to protect the endometrium in women with an intact uterus.

However, the use of progestogen has been associated with side effects, and breast discomfort is one of the most common problems. Breast discomfort can increase anxiety and lead to unnecessary interventions, which can lower satisfaction and compliance with MHT. In addition, concern about the increased risk of breast cancer related to progestin has been strongly emphasized since the Women's Health Initiative [2,3]. Experience of and concern about the side effects involving the breast are important reasons for discontinuance of MHT; therefore, these issues should be prioritized. Moreover, a regimen with fewer effects on the breast

is favorable for the provision of safe and convenient MHT.

Recently, a selective estrogen receptor modulator (SERM) was combined with conjugated estrogen (CE), and a new progestin-free tissue-selective estrogen complex (TSEC) was developed. Currently, a TSEC consisting of 0.45 mg CE and 20 mg bazedoxifene (BZA) is used in the management of vasomotor symptoms and prevention of osteoporosis.

The objective of this review was to evaluate the effects of the TSEC containing CE and BZA on the breast.

CONTENTS

Preclinical studies

Initially, the relative estrogen receptor (ER) agonistic and antagonistic effects of different SERMs, combined with various estrogens or administered alone, were compared in sexually immature ovariectomized female mice [4]. When measuring amphiregulin mRNA and

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morphological effects, BZA demonstrated less agonistic activity and a stronger antagonistic effect on CE, relative to raloxifene or lasofoxifene, in the mammary gland.

In addition, when comparing the effects of estradiol, CE, and BZA on mammary gland and breast cancer xenografts, BZA effectively blocked CE-stimulated estrogenic effects on ductal length, terminal end bud development, cell proliferation, apoptosis, and estrogen-responsive gene expression. In human xenografts, BZA inhibited tumor progression via estrogen [5]. Moreover, CE was much less potent than estradiol in terms of proliferation, apoptosis, and gene expression. These findings suggest that CE and BZA could block estrogen action in both benign and malignant breast tissue.

Further, in a preclinical trial, 95 ovariectomized cynomolgus macaques were randomly assigned to receive no treatment, BZA, CE, or BZA and CE with women's daily equivalent doses, and breast effects were compared after 6 months of treatment. The results showed that total epithelial density, lobular enlargement, and Ki67 immunolabeling in the terminal ducts were lower with CE and BZA, relative to CE alone. This combination also antagonized ER- α regulated genes significantly and reduced ER- α protein expression and markers of ER- α activity [6]. Clinically, these findings could support a lower breast-cancer risk profile for CE and BZA relative to those for other estrogen-progestin therapies.

To explore the mechanism of CE and BZA, the impact of gene expression and the recruitment of cofactor peptides to ER- α were compared across various estrogens with or without SERMs. CE was more potent than estradiol in mediating ER- α interaction with cofactor peptides, and a combination of CE and BZA showed maintenance of CE-dependent cofactor recruitment on estrogen-receptor α at lower efficacy, which differed from receptor confirmation shown with other SERMs [7]. This finding indicated that combinations of other estrogens and SERM preparations might not demonstrate the beneficial effects shown by CE and BZA.

Moreover, several studies have evaluated the effects of CE and BZA on human breast tissue, particularly in human breast cancer cell line MCF-7. In a GeneChip microarray to compare gene expression profiles of SERMs alone or combined with CE, different SERMs showed different gene expression patterns demonstrating differences in the ability to antagonize CE-induced

cell proliferation. Antagonistic activity was significantly higher with the combination of CE and BZA, relative to other SERMs [8].

When comparing estradiol and CE alone on proliferation and apoptosis, CE stimulated MCF-7 growth at a higher concentration relative to estradiol, and the stimulatory effects of CE on progesterone receptor and amphiregulin expression were weaker relative to those of estradiol. BZA effectively blocked the stimulatory actions of CE and reserved antiapoptotic action [9].

In addition, CE was less effective than estradiol in the recruitment of extracellular signal-regulated kinase2 and the stimulation of proliferation of breast cancer cells. Moreover, BZA antagonized CE stimulation of gene expression and cell proliferation in the TSEC [10].

The results of these preclinical studies indicated that agonistic and antagonistic activity was ideally balanced, and lack of breast stimulation was observed with a combination of CE and BZA. In addition, these findings demonstrated the antiestrogenic effects of the TSEC on breast tissue in postmenopausal women.

Clinical studies

The effects of the TSEC on the breast in clinical studies can be divided as follows: symptoms (breast pain or tenderness), markers (mammographic density), and clinical outcomes (breast lesion or cancer). Table 1 presents the results for the breast in five SMART (Selective estrogens, Menopause, And Response to Therapy) trials.

Breast pain or tenderness

Breast discomfort, such as pain or tenderness, is a common side effect of MHT and could be associated with the risk of breast cancer when it occurs after estrogen-progestin therapy [11].

In the main SMART-5 study, breast tenderness was reported in 3.4% of TSEC users; this rate was similar to that observed for a placebo (3.0%) and lower relative to that for CE 0.45 mg/medroxyprogesterone acetate 1.5 mg (10.9%). Moreover, none of the TSEC users discontinued the medication because of breast tenderness [12]. In the other SMART studies, SMART-1 to -4, breast pain or tenderness did not increase in TSEC users when compared to a placebo [13-16].

Further, in a recent retrospective cohort study, 82 postmenopausal women who switched to TSEC from other hormone therapies because of vaginal bleeding or breast discomfort were assessed. Of these women,

Table 1. TSEC and breast from SMART trials

Study	Number	Duration	Results, compared to placebo
SMART-1	TSEC: 433, placebo: 427	24 mo	Similar breast pain Similar breast cancer incidence No increase in breast density
SMART-2	TSEC: 127, placebo: 63	12 wk	Similar breast pain
SMART-3	TSEC: 219, placebo: 105	12 wk	Similar breast pain
SMART-4	TSEC: 361, placebo: 172	12 mo	Lower breast pain than conventional MHT
SMART-5	TSEC: 445, placebo: 474	12 mo	Similar breast pain Similar breast cancer incidence No increase in breast density

TSEC: tissue-selective estrogen complex, SMART: Selective estrogens, Menopause, And Response to Therapy, MHT: menopausal hormone therapy.

47.3% cited breast discomfort as the reason for the switch. Almost all women with breast discomfort or vaginal bleeding had experienced an improvement in symptoms following the switch from conventional MHT to the TSEC [17].

Breast density

Breast density is a well-known, independent risk factor for breast cancer [18]. In the Women's Health Initiative, estrogen alone was compared to estrogen-progestin therapy, which increased breast density by 4.9% after 2 years of use [19]. Although the association between increased breast density during MHT and breast cancer risk remains unclear, increased breast density during MHT could reduce the sensitivity and specificity of mammography and interfere with breast cancer screening. Therefore, MHT regimens with fewer effects on breast density would be favorable.

In an ancillary study of SMART-1, mammographic density reduced significantly after 24 months of TSEC use (−0.39%) in 129 women; this rate was similar to that for a placebo (−0.42%) and consistent with the expected decrease over time [20]. In addition, in a sub-study of SMART-5, no significant difference in breast density changes was observed between TSEC and placebo users after 12 months of treatment [21]. Moreover, in pooled data from five SMART trials, which included 1,585 TSEC users and 1,241 placebo users, CE and BZA did not increase breast density for up to 2 years, unlike CE and medroxyprogesterone acetate [22].

Breast lesions

In the SMART-4 study, the occurrence of adverse events involving the breast, such as breast cysts (0.3%, $n = 1$) and fibrocystic breast disease (0.6%, $n = 2$), did not differ between the TSEC and a placebo [16]. In the

main SMART-5 study, abnormal mammograms were observed in four women using TSEC (0.9%); this rate did not differ significantly from that with a placebo (0.2%, $n = 1$). In addition, the breast cancer rate for TSEC users was 0.4% ($n = 2$), which was similar to that for the placebo (0.2%, $n = 1$) [12]. Further, in pooled data from SMART-1, SMART-4, and SMART-5, the incidence rates for abnormal mammograms at 12 months with TSEC (2.6%) and placebo (3.2%) use were similar [22].

Moreover, a recent study assessed 1-year changes in the imaging of breast lesions following the switch from other hormone therapies to TSEC in women who had previously shown breast lesions. The results demonstrated that most breast lesions identified via ultrasonography or mammography (88.4%) remained unchanged after 1 year of TSEC use [17]. This finding, which is consistent with those of previous studies showing no difference in newly detected breast lesions during TSEC use, when compared with a placebo, emphasizes the safety profile of TSEC use for the breast.

However, breast cancer risk in TSEC users has not been established because of the small number of events and insufficient duration of clinical trials (up to 2 years). Nevertheless, in a pooled analysis of all 5 SMART trials, the relative risk of breast cancer for the TSEC was 1.1 (95% confidence interval, 0.3–3.8), which was similar to that for a placebo [22].

CONCLUSION

The TSEC containing CE and BZA is a new, progestin-free MHT. According to preclinical and clinical data, the TSEC does not stimulate the breast or increase breast density, the incidence of breast pain or tenderness, or the risk of breast cancer (Fig. 1). Con-

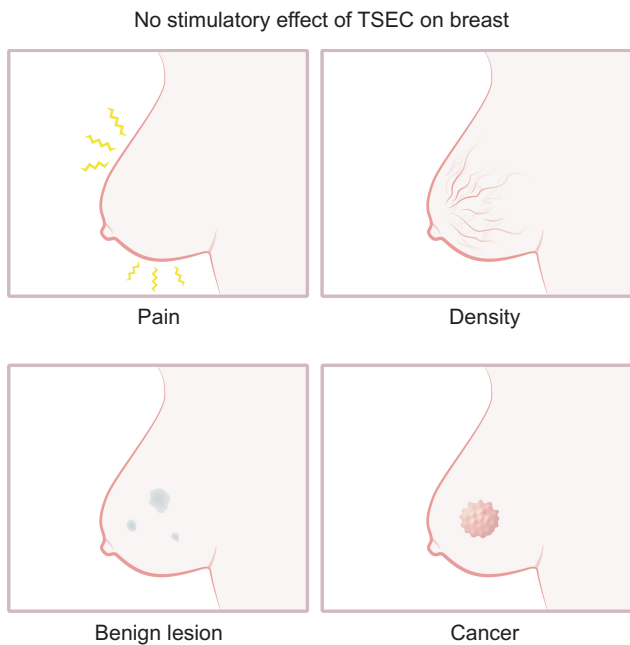


Fig. 1. No stimulatory effect of TSEC on breast.

sidering the efficacy and safety profile of the TSEC for the breast, it is promising in an era in which long-term MHT is favored for postmenopausal women.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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